Synchronous Balanced Analysis

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Overview

* What?

  Piecewise synchronous approximation of Chemical Reaction Networks' (CRN) dynamics

* Why?

  - highlight interdependence of cellular processes
  - finite cellular resource allocation VS cellular processes (i.e., growth)
  - rephrase mass action run of CRNs as an optimisation problem

* How?

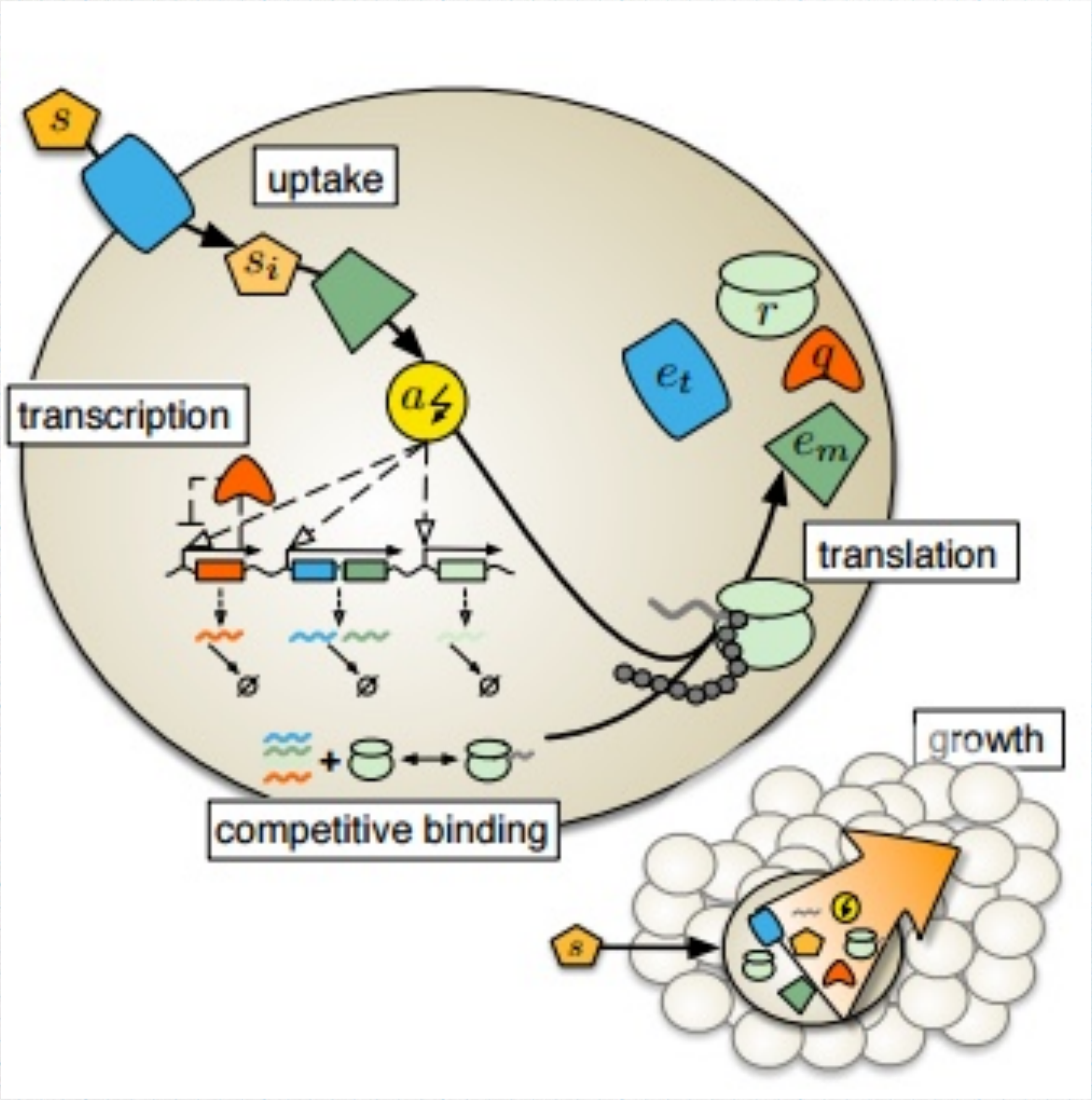
  Resource allocation centred Petri Nets with maximal-step execution semantics

* Usage?

  Approximation of real dynamics, constraint-based model similar to Flux Balance Analysis

Work in progress!

Motivation



Andrea Y. Weiße, Diego A. Oyarzún, Vincent Danos, and Peter S. Swain
Mechanistic links between cellular trade-offs, gene expression, and growth
PNAS 2015 112 (9) E1038-E1047; 2015, doi:10.1073/pnas.1416533112

Cellular processes rarely work in isolation: the rest of the cell cannot be ignored.

Finite cellular resources: committing to one task reduces the amount available to others

Define a formal notion of "growth": use as an improved biomass function in FBA

Modeling CRNs

CRN = $\langle S, \nabla^+, \nabla^-, R, \kappa \rangle$

PN = $\langle P, T, W, m_0 \rangle$

species

$\{S_1, \ldots, S_s\}$

reactions

$\{R_1, \ldots, R_r\}$

stoichiometry matrices

$$\nabla^+ \in \mathbb{R}^{r \times s}$$
$$\nabla^- \in \mathbb{R}^{r \times s}$$

reaction rate constants

$$\kappa : R \to \mathbb{R}_{>0}$$

places

initial marking

$$m_0 : P \to \mathbb{N}$$

transitions

$$\forall s, t : \nabla^-(s,t) = W(s,t)$$
$$\forall s, t : \nabla^+(s,t) = W(t,s)$$
$$\nabla = \nabla^+ - \nabla^-$$

$$W : ((S \times T) \cup (T \times S)) \to \mathbb{N}$$

CRN mass action dynamics

reaction: $$r_i : \sum_{j=1}^{s} \nabla^-_{ij} S_j \xrightarrow{k_i} \sum_{j=1}^{s} \nabla^+_{ij} S_j$$

reaction network: $$\nabla^- S \xrightarrow{k} \nabla^+ S$$

system state: $$x = (x_{S_1}, ..., x_{S_s}) \in \mathbb{N}^s$$

CRN dynamics: $$\frac{dx}{dt} = (\nabla^+ - \nabla^-)^T \cdot K \cdot x^{\nabla^-}$$

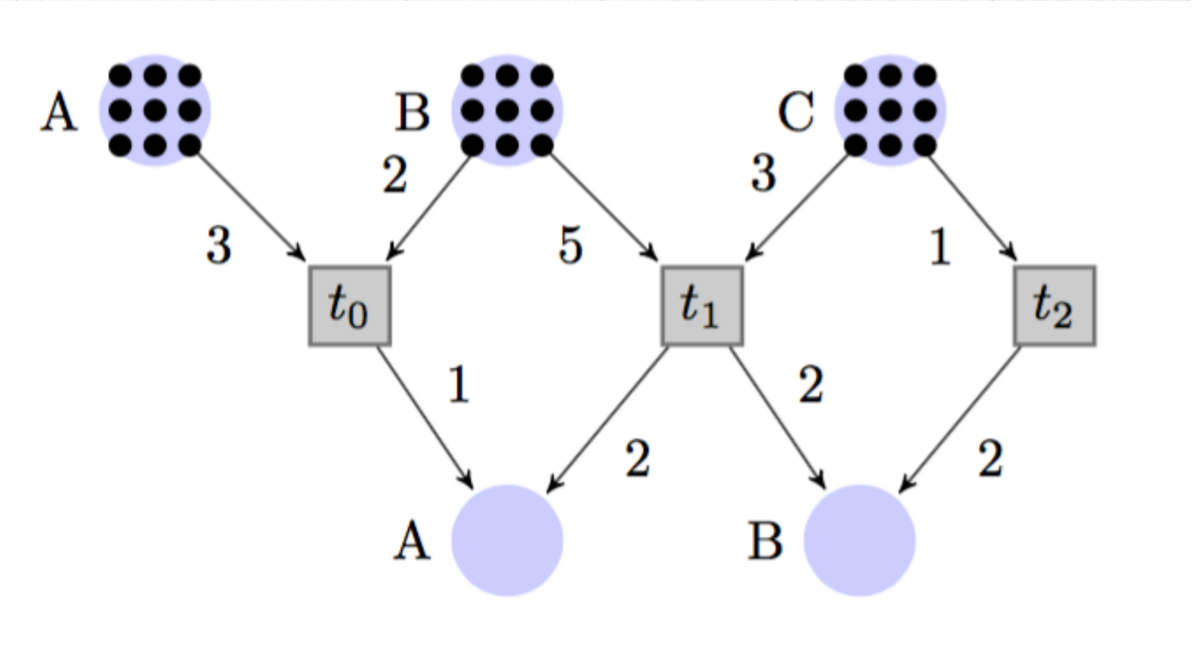
$K = diag(\kappa_1, ..., \kappa_r)$ vector-matrix exponentiation

Petri Nets & Chemical Reaction Networks

$$3A + 2B \xrightarrow{\kappa_0} A$$

$$5B + 3C \xrightarrow{\kappa_1} 2A + 2B$$

$$C \xrightarrow{\kappa_2} 2B$$

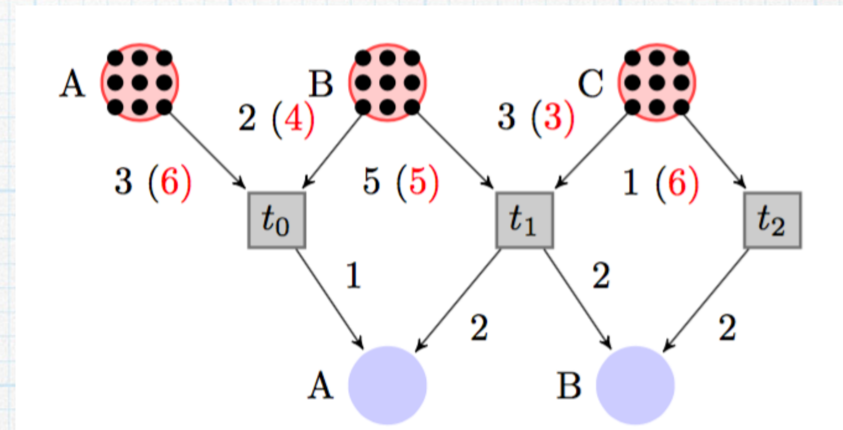


$$m_0 = (9, 9, 9)$$

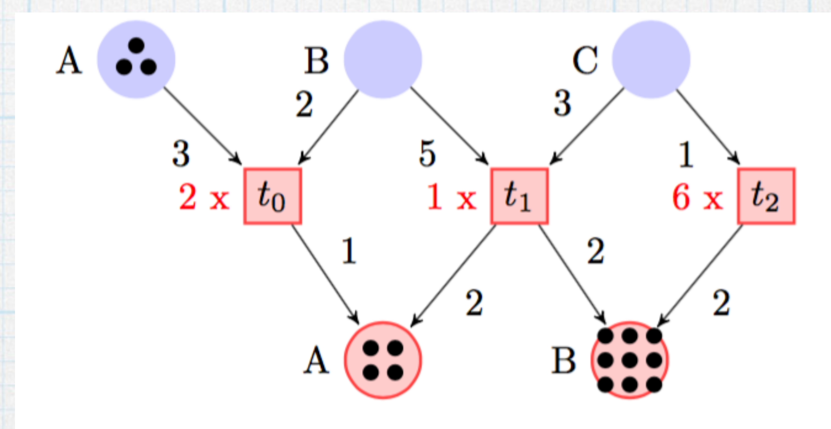
$$\nabla^- = \begin{bmatrix} 3 & 2 & 0 \\ 0 & 5 & 3 \\ 0 & 0 & 1 \end{bmatrix} \qquad \nabla^+ = \begin{bmatrix} 1 & 0 & 0 \\ 2 & 2 & 0 \\ 0 & 2 & 0 \end{bmatrix}$$

Piecewise synchronous execution

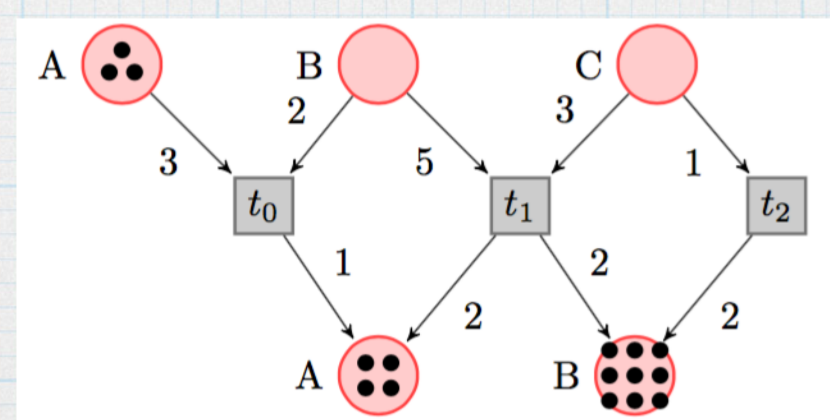
Split:



Burst:



Collect:



"SPLIT": resource allocation

Resource allocation matrix: α_{ij} (reaction: i, species: j)

$$\alpha \in \mathbb{R}^{|T| \times |S|}$$

$$\forall j \in S, \sum_{i \in T} \alpha_{ij} \leq 1$$

Interpretation: resource fraction VS reaction probability

"BURST": Max-parallel execution semantics of PN

"execute greedily as many transitions as possible in one step"

Definition:

A max-parallel execution step in a PN at state m is a positive T-vector v s.t.:

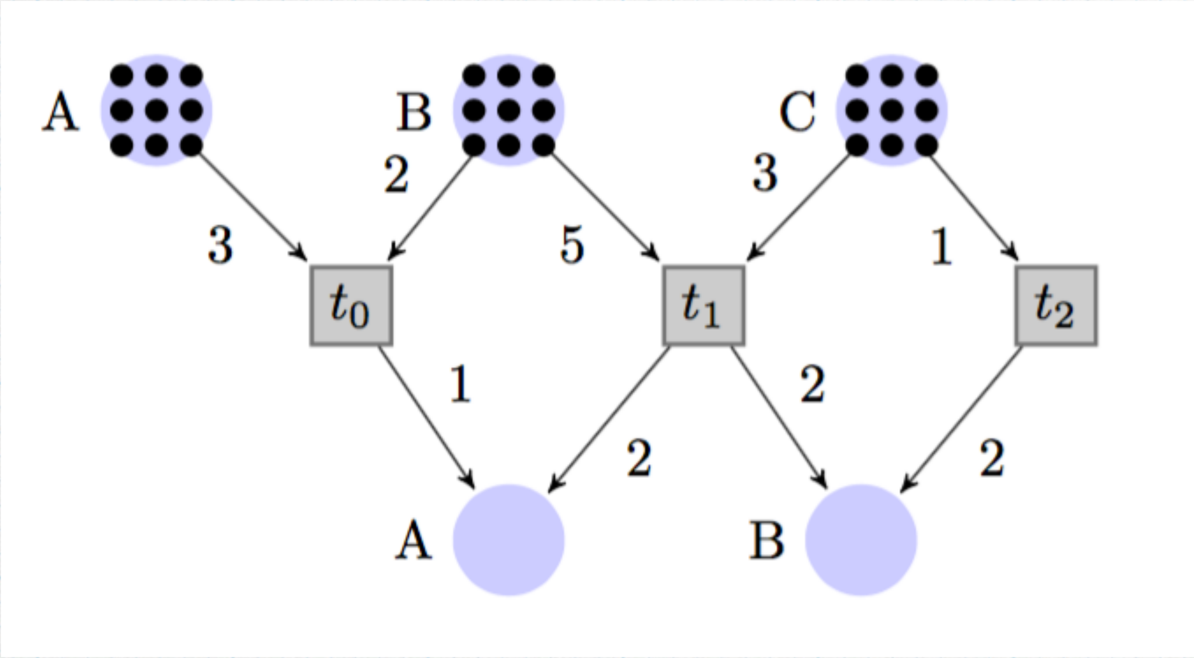
1. v is compatible with m:

$$0 \leq m - \nabla^{-} v$$

2. v is exhaustive:

$$\forall j \in T, m - \nabla^{-} v \ngeq r_j, \text{ where } r_j \text{ is the } j^{th} \text{ column of } \nabla^{-}$$

"BURST": Max-parallel execution semantics of PN



$$\{t_0 \times 3, t_2 \times 9\}$$

$$\{t_0 \times 2, t_1, t_2 \times 6\}$$

Resource allocation & Max Parallel Execution

Define $$(\alpha \star m)_j = \min_{i \in S}\left(\frac{\alpha_{ji}}{\nabla^-_{ij}} \cdot m_i\right)$$

Theorem: $\forall v$ compatible with a resource array m (and potentially max-parallel), $\exists \alpha$ resource allocation matrix s.t. $v = \alpha \star m$. Furthermore, if the CRN is unary, there is unicity of α

Our execution semantics encompasses max-parallel execution

Growth in unary CRNs

State of the system after 1 execution with given α split:

$$(I + \nabla \cdot \alpha) \cdot m$$

State of the system after **k** executions with given α split:

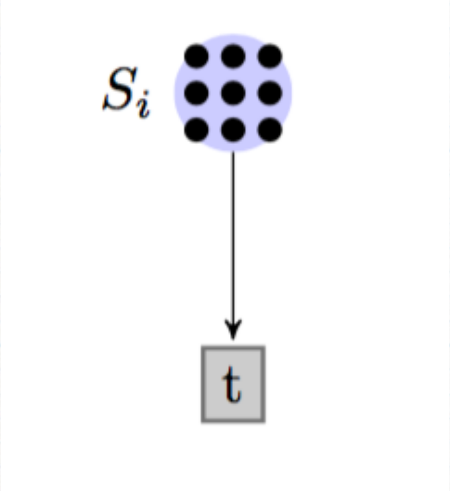
$$D_\alpha^k \cdot m, \ \text{with} \ D_\alpha = I + \nabla \cdot \alpha$$

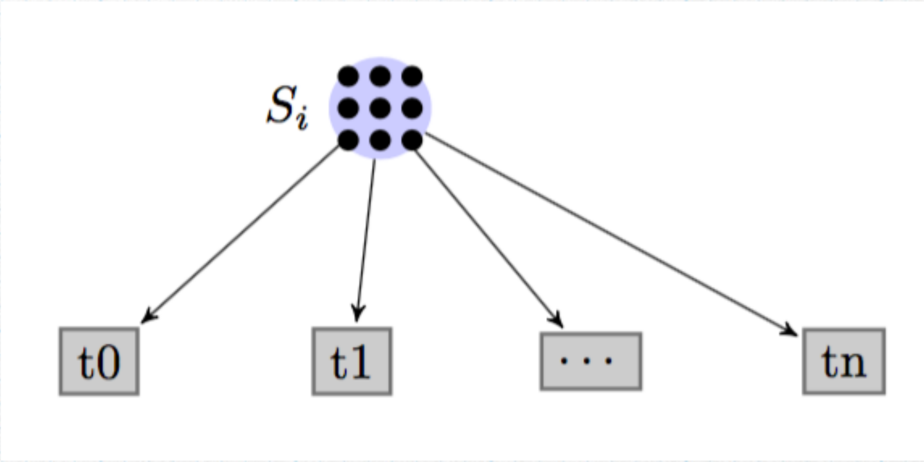
$\lambda_1 > \lambda_2 > \cdots$, the eigenvalues of D_α $\qquad m = \sum_i m_i, \ \text{with} \ m_i \in E(\lambda_i)$

$$D_\alpha^k \cdot m = \lambda_1^k \cdot [m_1 + \sum_{i \geq 2} (\frac{\lambda_i}{\lambda_1})^k \cdot m_i]$$

The growth rate of the system is given by λ_1.

Unary CRNs and Depletion Time





$$S_i \to \ldots @k$$

$$\tau = k^{-1} \log(\frac{S_i(0)}{s_i})$$

$$S_i \to \ldots @k_j; j \in N_i, |N_i| = n$$

$$\tau_j = k_j^{-1} \cdot \log(\alpha_{ji} \cdot \frac{S_i(0)}{s_{i,j}})$$

depletion level

Unary CRNs: “iso” assumptions

Decouple production and consumption

Isochronous: $\forall j \in N_i, \tau_j = \tau$

Iso-remainder: $\forall j \in N_i, s_{i,j} = s_i$

$$\Delta m(\tau) = \nabla \cdot (\alpha\_i - \epsilon\_i) \cdot m$$

$$\frac{\Delta m}{\tau} \approx^{\tau \to 0} \nabla \cdot [k_j] \cdot m$$

The usual ODE dynamics is recreated: $\dfrac{dx}{dt} = (\nabla^+ - \nabla^-)^T \cdot K \cdot x^{\nabla^-}$

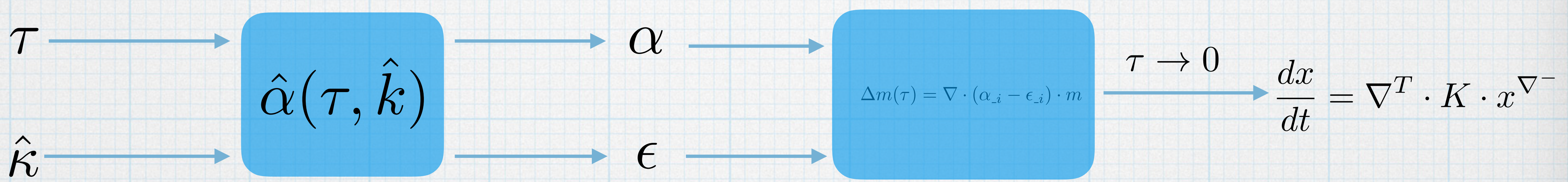
Unary CRNs: "iso" assumptions

$$\hat{\alpha}_{S_i}(\tau, \hat{k_{S_i}}) = [\alpha_{\_i} - \epsilon_{\_i}] = [\frac{e^{\tau \cdot k_j} - 1}{\sum_j 1 + e^{\tau \cdot k_j}}]$$

Resource allocation matrix as a function of depletion time and reaction rate constants!

Concrete interpretation

Approximation of system dynamics:



- temporised discrete execution
- "don't wait for the slowest reaction"
- simulation: big step approx. of an integrator (deterministic tau-leaping)

Abstract interpretation

Synchronous Balanced Analysis

Objective function: λ_1

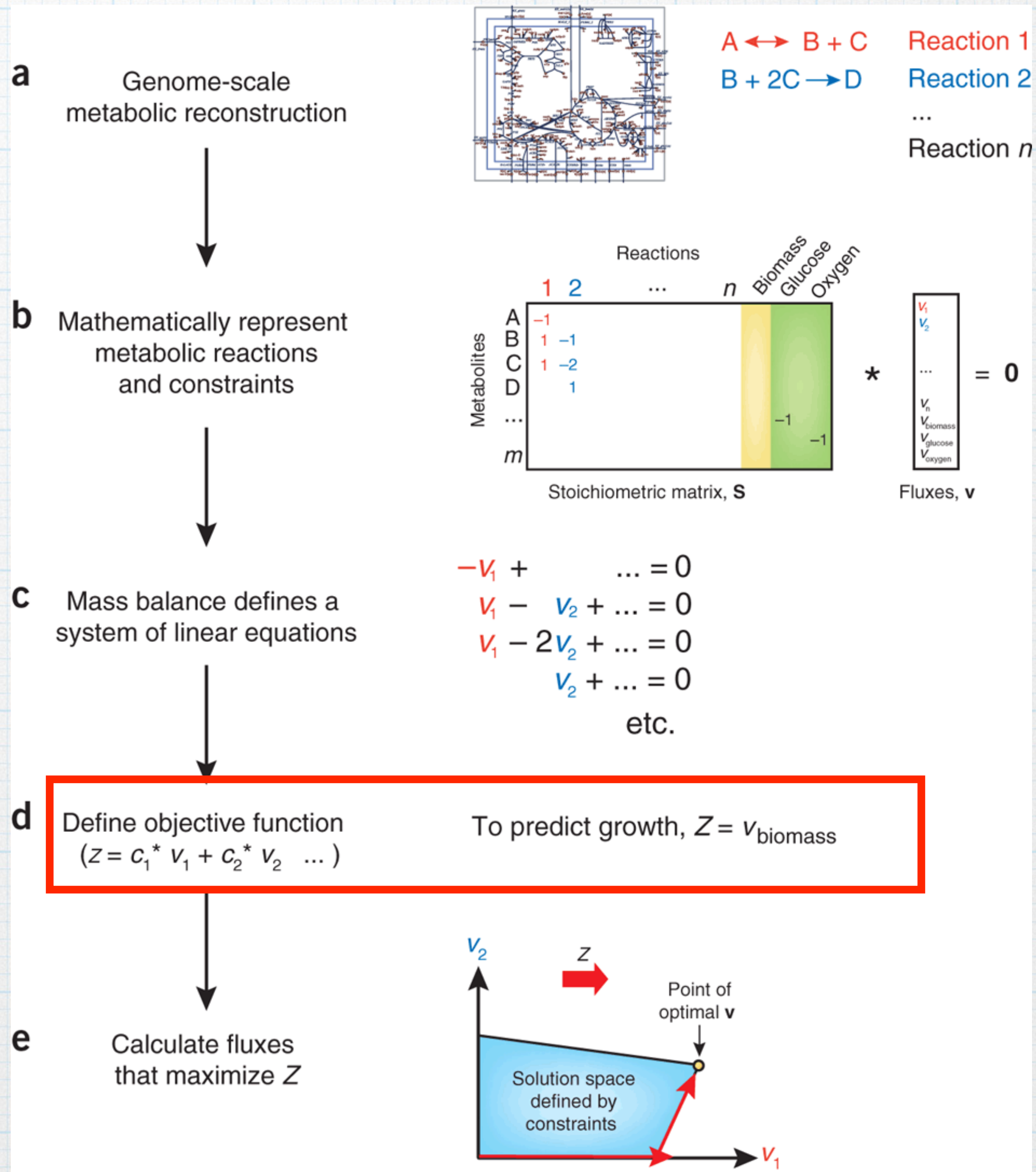
$$D_\alpha^k \cdot m = \lambda_1^k \cdot [m_1 + \sum_{i \geq 2} (\frac{\lambda_i}{\lambda_1})^k \cdot m_i]$$

maximize

α_{max}

$\hat{\alpha}(\tau, \hat{k})$

Constrain reaction rates, refute models



SBA VS.FBA

- able to handle growth (no steady state assumption needed)
- take into account real system kinetics
- characterise behaviour of a cell using only one construction: α
- replace mechanistic details of resource allocation with an abstract vector
- objective biomass function emerges directly from method: growth rate
- maximising biggest eigenvalue of matrix: how ?

Future work

- **binary reactions**: depletion time? (Michaelis-Menten type assumption)

- explore correlations between growth rate and model parameters

- tau-leaping, whole-cell models by Karr, etc...

Conclusion

Piecewise synchronous approximation of the dynamics of (growth) CRNs:

parallel execution semantics of PN, based on resource allocation .

Interpretations:

1. approx. of real system dynamics
2. constraint based method (like FBA)

Thank you!